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EXAMINER				
SGAGLAS, MAGDALENE K				
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1632				
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary

Application No.

10/518,749

Applicant(s)

NAKAYAMA ET AL.

Examiner

Magdalene K. Sgagias

Art Unit

1632

Period for Reply -- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 10 March 2010.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1 and 3-18 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1 and 3-18 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 22 December 2004 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/SB-06)
Paper No(s)/Mail Date 03/10/2010
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

Applicant's arguments filed 03/10/2010 have been fully considered but they are not persuasive. The amendment has been entered. Claims 1, 3-18 are pending and under consideration. Claims 2 and 19 have been canceled.

The IDS filed on 03/10/2010 has been considered.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The rejection of claims **1, 3-4, 8-12, 13-18** under 35 U.S.C. 103(a) as being unpatentable over **Tropepe et al** (Neuron, 30: 65-78, April, 2001); **Weiss et al**, (US 5,981,165) in view of **Suemori et al** (Developmental Dynamics, 222: 273-279, 2001) is maintained for the reasons of record 12/10/2009.

Applicants argue each reference individually. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

A. Applicant's argue Tropepe discloses a neurosphere, not a stem cell sphere as claimed, and the methods are fundamentally different. The Specification discloses that methods of making a neurosphere are known within the art. (Specification, page 2, line 17). However the presently claimed methods generate stem cell spheres. The differences between the two are disclosed in the Specification at page 2, line 2 to page 3, line 8. In particular, embryonic neurospheres are cultured with a defined medium, and while it has self-renewal capabilities, the ultimate population of differentiated neural cells arises from a small portion of the total population of neural stem cells. In contrast, the present invention requires culturing in an undefined medium (astrocyte conditioned medium), where the cells of the stem cell sphere migrate from the SCS as neural stem cells in large quantities.

These arguments are not persuasive because the embryonic stem cell spheres of Tropepe meet the required method steps of the instant claims as broadly claimed and each limitation is cited in the rejection. The embryonic stem cell spheres of Tropepe are grown in a culture suspension under conditions as instantly claimed for 7 days where the embryonic stem cells at different stages reach the stage of commitment to a neural stem cell and then into neural cells. In contrast to applicant's arguments the instant claims are not limited to where the cells of the stem cell sphere migrate from the SCS as neural stem cells in large quantities. Therefore, Tropepe's embryonic stem spheres provide the method steps for differentiation of embryonic stem cells into neural stem cells and then into neural cells and the growth conditions of a medium equivalent to the conditioned medium as instantly claimed since the end result is the production of neural cells. Tropepe provides the source of embryonic stem cells to create the embryonic stem cell suspension of sphere under the required growth conditional medium however, because Tropepe teaches that over time the embryonic stem cell sphere differentiate into a neural stem cell sphere and neural stem cells are still grown as neurospheres or the

neural stem cells start to be committed to differentiate into neural cells and the neural cells are grown as neurospheres since the embryonic stem cell sphere are differentiated into neural cells Tropepe's neurospheres after the culture of embryonic stem spheres does not exclude the fact that Tropepe teaches the growth of embryonic stem cell spheres as instantly claimed.

Applicants argue Tropepe clarifies that the ES cells are differentiated into Nestin+, III-tubulin+, and NeuN+ cells in the absence of an exogenous factor within 24 hours (page 71, the entire section of "Neural Cell Fate Is Rapidly Established from ES Cells in the Absence of Exogenous Factors"). This description suggests a possibility that the ES cells autonomously differentiate into neural cells (page 74, second column, the section of "Default Neural Cell Fate Specification during Mammalian Development," 4 to 9 lines from top of the first paragraph of this section). One of ordinary skill in the art cannot expect a method of differentiating neural stem cells and neural cells using a liquid factor contained in ACM from the experimental results of Tropepe and interpretations drawn therefrom. Moreover, Tropepe concludes that the LIF upon formation of the colony acts as a permissive factor to maintain the ES cells in an undifferentiated state (pages 68-69, the whole section of "LIF Functions as a Permissive Factor for Neural Stem Cell Differentiation of ES Cells"; especially, the sentence that reads: "Thus, LIF is critical ... in these minimal conditions" on page 69, first column, lines 9-12 of Tropepe). Furthermore, Tropepe clarifies that the colony formation is carried out in the presence of LIF by reacting the ES cells themselves to endogenous FGF-2 secreted by the ES cells (page 68, first column, 3 lines from bottom to page 69, first column, line 5). But, in the present invention, LIF is not added to ACM exogenously. In addition, in the SCS method of the present invention, FGF-2 (bFGF) acts to proliferate the neural stem cells. Therefore, in the present invention, the differentiation of the neural stem cells is carried out under a completely different technical idea from that of Tropepe.

These arguments are not persuasive because the instant claim 1 as broadly claimed requires the growth of embryonic stem cells in suspension or spheres for a period of 7 to 15 days but it does not require a timeline for the differentiation of embryonic stem cell spheres into neural stem cells or neural cells. Therefore, Tropepe's embryonic stem cells differentiation into Nestin+, III-tubulin+, and NeuN+ cells in the absence of an exogenous factor within 24 hours embraces the timeline of the instant invention for the beginning of embryonic stem cells to start to differentiate into neural stem cells or neural cells since the cells are grown in suspension for the required period of 7 to 15 days. Second, the instant claims require ingredients equivalent to the conditioned medium to directly produce isolated neural cells, therefore, since the end result is the production of neural cells using said conditioned medium and since Tropepe teaches the differentiation of embryonic stem cells into neural cells by exogenously adding LIF that results in the production of neural cells then, one of ordinary skill in the art can expect a method of differentiating neural stem cells and neural cells using LIF as a liquid factor contained in the medium in contrast to applicant's assertion of the mechanism of action of LIF by reacting the ES cells themselves to endogenous FGF-2 secreted by the ES cells.

Applicants argue Tropepe only discloses a method for proliferating neural stem cells by preparing a colony equivalent to a neurosphere from relatively small numbers of ES cells. One of ordinary skill in the art could not expect the differentiation of a colony of undifferentiated ES cells directly into neural stem cells or neural cells as taught in the present invention from the teachings of Tropepe. Also in the ES-derived spheres of Tropepe, the gene expression of GATA4, brachyury, and CK- 17 is different from the cells obtained in the present method. Compare (Fig. 2-B) of Tropepe with Figure 23 of the present method. In Figure 2B of Tropepe, the ES (primary ES cells), SC (ES-derived sphere colonies, and + (positive tissue control) might be compared to Figure 23 column 1 (undifferentiated embryonic stem cells, Specification, page

5, line 23), column 2 (the SCS formed by carrying out the suspension culture, *Id.*) and column 3 (the cell masses obtained by carrying out the adhesion culture). It is clear that the brachyury and CK-17 expression is significantly different between the cell populations, and that the GATA4 expression is likely different as well.

These arguments are not persuasive because regardless of the relative number of ES cells as a source of the method steps as required for the differentiation of stem cells into neural stem cells or neural cells the same method steps result in the same end product which is the production of neural cells as taught by Tropepe and as instantly claimed. The instant claims do not require a timeline for the expression of neural stem cell markers or neural cell surface markers, therefore, Tropepe's teachings of neural cell surface markers within 7 days embraces the instant invention.

B. Applicants argue Weiss does not change the fundamental method disclosed in Tropepe. Applicants argue first, like Tropepe, Weiss also discloses the neurosphere method. Second, Weiss discloses a completely different origin of the cells, such that one of skill would not apply the teachings of Weiss to Tropepe. Third, Weiss does not disclose an astrocyte conditioned medium or a medium equivalent to ACM. Fourth, Weiss teaches away from the omission of FGF. As a preliminary matter, Applicants submit that Weiss is a development group for the neurosphere method discussed in the Specification, beginning at page 2, line 14 (Reynolds and Weiss, *Science* 255: 1707, 1992, Reynolds et al., *J. Neurosci* 12: 4565, 1992, which refer to the method of column 12, lines 29-31 of Weiss)(both attached), and the method of Weiss is carried out using the medium of the Reynolds neurosphere method (column 8, last paragraph of Weiss).

These arguments are not persuasive because Weiss is not cited for the source of embryonic stem cells since Tropepe sites the source of embryonic stem cells but Weiss is cited

to supplement the teachings of Tropepe for culturing the SCS obtained from Tropepe (step A) in the state of adhesion of SCS to an adhesive culture substratum carrying a cell adhesion molecule in the absence of bFGF and in the presence of an astrocyte conditioned medium or ingredients equivalent to the conditioned medium thereby obtaining a neuron that expresses tyrosine hydroxylase as required in claims 8-14 (emphasis added). Weiss teaches medium in the state of adhesion of the neural stem cells to an adhesive culture substratum by plating the cells onto poly-L-ornithine coated glass cover slips, in the complete medium with rat B49 glial cell line-derived conditioned medium in the absence of bFGF, in the presence of FGF2 and in the presence of ingredients substantially equivalent to astrocyte conditioned medium (example 8). Weiss teaches the isolated neuron expresses tyrosine hydroxylase (example 2) (claim 14) (emphasis added).

Applicants argue the cells that are prepared in Example 3 of Weiss are somatic neural stem cells, not neural stem cells prepared from embryonic stem cells. In addition, the conditions in which TH exist in the neurosphere prepared in Example 3 is a conditioned medium (BCM) + FGF-2 (column 15, line 9), "in the absence of bFGF" as suggested by the Examiner. Furthermore Weiss teaches away from the present method of obtaining neurons as in claim 12, which excludes bFGF, by suggesting that BCM and FGF-2 are required. Weiss confirms that neural stem cells from an adult subventricular zone are differentiated into TH+ neurons, so that it is thought that a possibility of preparation of TH+ neurons not only from fetal tissues but also from adult brain is taken into consideration with autografts from patients with a Parkinson's disease in mind (column 3, lines 44-48). However, this is the differentiation from adult neural stem cells in the presence of BCM and FGF-2. This teaching away is supported by the disclosure of Examples 6 and 8 in Weiss. It is evident from Example 6 of Weiss that in Paradigm 1 in which ability of ACM and BCM to induce differentiation into TH+ neurons is evaluated using

an embryonic cortical primary culture, and Paradigm 2 in which the ability on an astrocyte feeder layer is evaluated, the differentiation does not take place unless FGF is present (columns 13-14, TABLES I and II). Also, in Example 8 where similar effects are evaluated with the neurosphere prepared in Example 3, the necessity of FGF-2 is confirmed in Weiss. Therefore, the present invention teaching the differentiation into neural stem cells or neural cells from ES cells in the presence of ACM alone could not be expected from the teachings of Weiss.

As discussed above Weiss is not cited for the source of embryonic stem cells since Tropepe teaches the culture of embryonic stem cells and since the instant claims as broadly claimed do require a timeline when the SCS are committed to neural stem cells or neural cells Weiss teachings of complete medium with rat B49 glial cell line-derived conditioned medium in the absence of bFGF, in the presence of FGF2 and in the presence of ingredients substantially equivalent to astrocyte conditioned medium (example 8) which result in the isolated neuron express tyrosine hydroxylase (example 2) (claim 14) (emphasis added) thus one of ordinary skill in the art will use the culture ingredients of Weiss to induce differentiation of SCS into neural stem cells and then into neural cells expressing tyrosine hydroxylase in the culture system of Tropepe.

C. Applicants argue the addition of Suemori does not remedy the deficiencies of Tropepe and Weiss. Suemori is cited for the disclosure of methods of monkey embryonic stem cell culture. Applicants note that the citation referred to by the Examiner is merely a discussion in Suemori citing another paper, by Thomson et al., Science 282:1145-7, 1998., 1145, second column, lines 12-15.

The Suemori publication focuses on the fact that ES cells of monkey can be maintained in an undifferentiated state for a long period of time, and then differentiated into various types of tissues.

The differentiation of ES cells in Suemori is by an embryoid body method (page 275, first column, Figure 2). Therefore, Applicants submit that the content of Suemori is not relevant to the presently claimed method. Furthermore, any suggestions of applying the method of Suemori to human ES cell therapies are again not relevant to the claimed method. Furthermore, the cryopreservation in Suemori is of a different cell type. Specifically, Suemori discusses that cynomolgous ES cells can be cryopreserved (page 274, second column, 2 lines from bottom to page 275, first column, line 1). This is different from claim 12 of the present application where neural stem cells are cryopreserved. The two are at a different stage of differentiation.

These arguments are not convincing because Suemori is cited for the deficiency of culturing primate embryonic stem cells and not for the stage of differentiation of the SCS. Regarding the stage of cell cryopreservation Suemori et al teach the derivation of ES cell lines from the rhesus monkey (*Macaca mulatta*) and common marmoset (*Callithrix jacchus*) with shared many characteristics with human ES cells and the cynomolgus monkey, as well as the rhesus monkey, belong to the Catarrhini, which are closely related to humans; cynomolgus monkey ES cells could be maintained for long periods as stem cells, and they showed differentiation in vitro and in vivo into various tissues and the cells were cryopreserved, thus Suemori inherently teaches cryopreservation of neural stem cells since they are closely related to humans and it well known in the art teh cryopreservation of human neural stem cells.

The rejection of Claims 5-7 under 35 U.S.C. 103(a) as being unpatentable over Tropepe et al Neuron, 30: 65-78, April, 2001); Weiss et al, (US 5,981,165) in view of Vitkovic et al. (AIDS Res and Human Retroviruses, 7(9): 723-727, 1991) when taken with Reubinoff et al. (Nature Biotechnology, 19:1134-1140, 2001 (IDS)) when taken with

Thomson et al. (Science, 282:1145-1147, 1998) is maintained for the reasons of record 12/10/2009.

D. Applicants argue the combination of Vitkovic, Reubinoff, and Thompson.

Applicants argue each reference individually. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

a. Applicants argue the ACM of the present inventive method is different from that used in Vitkovic.

Applicants submit that the ACM used in Vitkovic is different from the ACM used in the present method, such that the combination of this medium with the methods of Tropepe and Weiss is not an ACM or a medium equivalent thereto. Specifically, the ACM used in Vitkovic contains sera, and with or without a reactive component obtained by lipopolysaccharide stimulation. The astrocyte-conditioned medium used in Vitkovic is prepared according to a publication made reference therein (Ref. 12: Vitkovic et al., J. Neuroimmunol 30: 153-60, 1990) (attached). The Vitkovic 1990 publication describes that astrocytes are cultured in a serum-containing medium (page 154, second column, the section of "Material and method, Culture media," lines 7-10). Further, astrocytes are stimulated by adding a lipopolysaccharide (page 155, first column, the section of "Preparation of astrocyte-conditioned supernatant," lines 1-8). Therefore, the ACM used in Vitkovic contains sera, and with or without a reactive component obtained by lipopolysaccharide stimulation. On the other hand, the ACM used in the present invention is prepared based on a serum-free, defined medium and DMEM/F12/1% N2 supplement (Nakayama and Inoue, Methods in Molecular Biology 330: 1-13, 2006: page 3, 2.1.1. Media 3.;

page 6, 3.1.5.2. Production of Astrocyte-Conditioned Medium)(attached), in which the influence of the sera to the ES cells is removed.

Accordingly, one of skill in the art would have no reasonable expectation of success in combining the fundamentally different methods of Tropepe and Weiss with the significantly different medium of Vitkovic to obtain the cell population obtained by the claimed method.

b. Like Weiss, Reubinoff teaches away from the omission of bFGF.

Applicants submit that Reubinoff teaches away from the presently claimed method and would not give one of skill in the art any reasonable expectation of obtaining a neuron in the absence of bFGF. Reubinoff describes that in order to commit the differentiation of the spheres from the generated ES cells to glial lineage, the medium is supplemented with PDGF-AA, bFGF, and EGF, followed by culture in the presence of T3 (page 1139, second column, lines 22-27). Also, Reubinoff points out the importance of bFGF and PDGF-AA in the enhancement of the proliferation of the glial precursor (page 1136, second column, lines 34-41, quoted ref. 14: Brustle et al., Science 285: 754-756, 1999; page 754, second column, lines 4-7). The differentiation into astrocytes as described in Reubinoff is carried out according to a conventional method using bFGF and PDGF-AA. Therefore, it would not be obvious for one of ordinary skill in the art to expect the present invention in which the spheres are differentiated into astrocytes in a Defined medium (Neurobasal/B27 supplement) alone in the absence of bFGF from the method of Reubinoff.

c. One of skill would not have any reasonable expectation of success based on the general speculation in Thompson. Applicants submit that the citations relied on by the Examiner from Thompson are merely speculation by the authors and would not provide any reasonable expectation of success to one of skill in the art. Specifically, the description on the paragraph bridging pages 1146 and 1147 of Thompson is merely mentioning an expectation as

a matter of course that specialized cells can probably be generated from the ES cells once the mechanism of the differentiation from the ES cells is elucidated. Also, the applications of the generated cells from human ES cells, the development of drugs and the applications to the transplantation therapies and the like are merely general descriptions. Accordingly, Applicants submit that one of skill in the art would not find the present inventive method obvious from the general speculation in Thompson.

These arguments are not persuasive because the combination of Vitkovic, Reubinoff, and Thompson is cited to cure the deficiency of step (B) which requires the presence of bFGF. Vitkovic, is cited for the use of culture medium containing bFGF and not for the presence of other growth factors of serum as applicants assert. In addition, Reubinoff supplements the teachings of Vitkovic, by teachings the use bFGF inhuman ES cells and moreover, Thompson Thomson teach that directing differentiation of ES cells to specific cell types for therapeutic use and since Suemori teaches shared many characteristics between human ES cells and the cynomolgus monkey, as well as the rhesus monkey, which are closely related to humans then it is obvious for one of ordinary of skill in the art to use bFGF under the culture conditions of Tropepe/Weiss since the instant claims require no timeline of adding the bGF or timeline for obtaining neural stem cells before they differentiate into neural cells for obtaining neural cells as instantly claimed. Therefore, one of ordinary of skill in the art would have been motivated to include bFGF in the culture medium of Tropepe/Weiss as taught by Vitkovic since Suemori/Reubinoff teach the similarities of primate and human ES stem characteristics for in vitro differentiation into neural stem cells for obtaining neural cells.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Magdalene K. Sgagias whose telephone number is (571) 272-3305. The examiner can normally be reached on Monday through Friday from 9:00 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, Jr., can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

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